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9

WO 03/035849 A3

(54) Title: METHODS FOR GENE TRANSFER USING PSEUDOTYPED LENTIVIRUSES

(57) **Abstract:** Methods for introducing nucleic acid sequences into hepatocytes, brain glial cells and airway epithelial cell are provided. The methods use filoviral and togaviral glycoprotein-pseudotyped lentiviruses. The viruses comprise a lentiviral capsid and a viral envelope further comprising a lipid bilayer and a functional filoviral glycoprotein or two functional togaviral glycoproteins. In one embodiment the lentivirus is a feline immunodeficiency virus (FIV). In an alternate embodiment, the filoviral glycoprotein is a Marburg virus glycoprotein. In another embodiment, the Marburg virus glycoprotein can have a mutation in the C-terminal portion of the amino acid sequence that results in a higher titer production of the pseudotyped virus. In an alternate embodiment the togaviral glycoproteins are alphavirus glycoproteins, for example, the E1 and the E2 envelope glycoproteins of Ross River virus (RRV).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/34545

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 63/00; C12N 15/00, 15/63
US CL : 424/93.1, 93.2, 93.21; 435/320.1, 455

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/93.1, 93.2, 93.21; 435/320.1, 455

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN, BIOSIS, CAPLUS, MEDLINE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/08131 A2 (PURDUE RESEARCH FOUNDATION) 17 February 2000 (17. 02. 2000), abstract, pages 10, 12, 15, 20-22, 49, 50.	5, 6, 8, 10-13, 15, 16, 18, 20-23, 25, 26

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
*	Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
09 April 2003 (09.04.2003)

Date of mailing of the international search report

10 JUL 2003

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/34545

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/34545

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9 and 15-19, drawn to a pseudotyped lentivirus comprising a lentiviral capsid, a lipid bilayer, and a Marburg glycoprotein having the cited mutations, and a method of introducing a nucleic acid encoding a desired protein into an airway epithelial cell by transducing the epithelial cell with a pseudotyped lentivirus comprising a lentiviral capsid, a lipid bilayer surrounding said capsid, a filoviral glycoprotein dispersed in said bilayer, and a nucleic acid encoding a desired protein.

Group II, claim(s) 10-14 and 20-26, drawn to a method of introducing a nucleic acid encoding a desired protein into a hepatocyte or a brain glial cell, or a liver or brain in a mammal by transducing the said cell with a pseudotyped lentivirus comprising a lentiviral capsid, a lipid bilayer surrounding said capsid, at least two different togaviral glycoproteins dispersed in said bilayer, and a nucleic acid encoding a desired protein.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: They are drawn to different scientific considerations by using different pseudotyped lentiviruses: a pseudotyped lentivirus comprising a filoviral glycoprotein or Marburg glycoprotein having cited mutations dispersed in the lipid bilayer vs a pseudotyped lentivirus comprising at least two different togaviral glycoproteins dispersed in the lipid bilayer, and transducing said lentiviruses into different types of cells or target sites: airway epithelial cells vs hepatocyte and brain glial cells or liver and brain. Therefore, they are drawn to different methods that differ at least in process steps, reagents and dosages used, schedules used, response variables, and criteria of success. Thus, groups I and II do not relate to a single general inventive concept under PCT Rule 13.1.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 3220-71692	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/34545	International filing date (day/month/year) 28 October 2002 (28.10.2002)	(Earliest) Priority Date (day/month/year) 26 October 2001 (26.10.2001)
Applicant MCCRAY, PAUL B.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
 - a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
 - b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
 contained in the international application in written form.
 filed together with the international application in computer readable form.
 furnished subsequently to this Authority in written form.
 furnished subsequently to this Authority in computer readable form.
 the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. Certain claims were found unsearchable (See Box I).
3. Unity of invention is lacking (See Box II).
4. With regard to the title,
 - the text is approved as submitted by the applicant.
 - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. _____
 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.

None of the figures